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Magnetic Resonance Characterization of Ischemic Tissue Metabolism

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Abstract: Magnetic resonance imaging (MRI) and spectroscopy (MRS) are versatile diagnostic techniques capable of characterizing the complex stroke pathophysiology, and hold great promise for guiding stroke treatment. Particularly, tissue viability and salvageability are closely associated with its metabolic status. Upon ischemia, ischemic tissue metabolism is disrupted including altered metabolism of glucose and oxygen, elevated lactate production/accumulation, tissue acidification and eventually, adenosine triphosphate (ATP) depletion and energy failure. Whereas metabolism impairment during ischemic stroke is complex, it may be monitored non-invasively with magnetic resonance (MR)-based techniques. Our current article provides a concise overview of stroke pathology, conventional and emerging imaging and spectroscopy techniques, and data analysis tools for characterizing ischemic tissue damage.

Keywords: MRI; MRS, cerebral ischemia, stroke; metabolism.

1. INTRODUCTION

Ischemic brain tissue damage mechanisms are complex, and have been categorized into pathophysiology, biochemistry, gene expression, cell signaling, pharmacology, and neuroimaging changes [1-3]. Magnetic resonance (MR)-based techniques have been playing a vital role not only to assist our understanding of stroke pathology but also to help guide stroke patient management [4-10]. As such, it is important to define relevant pathophysiologic mechanisms in stroke as determined by molecular and functional neuroimaging, identify and prospectively validate surrogate imaging biomarkers of tissue injury for early prediction of tissue outcome, and ultimately guide individualized stroke treatment, both in experimental stroke models and translational clinical investigation [11-13]. Our article provides a concise overview of stroke pathology, conventional and emerging MRI and MRS techniques, and multi-parametric data analysis tools that characterize the hemodynamic, metabolic, structural impairments subsequent to ischemic injury.

2. ISCHEMIC STROKE TISSUE DAMAGE

Ischemic stroke occurs when a major cerebral artery becomes blocked, causing severe hypoperfusion to the brain. Blood clots are the most common cause of artery blockage and brain infarction. After ischemic stroke brain tissue ceases to function and latterly suffers irreversible injury possibly leading to death of the tissue, i.e., infarction. Upon ischemia, tissue becomes low in energy substrates including

glucose and oxygen, and resorts to anaerobic respiration. Anaerobic glycolysis, however, produces less adenosine triphosphate (ATP) yet releases lactic acid as a byproduct. Lactic acid is an irritant and at high concentration, could further disrupt tissue metabolism and potentially destroy cells [1]. The major cascade of neuronal injury and brain infarction after ischemic stroke is initiated when the energy production such as ATP fails, leading to failure of energy-dependent processes (such as ion pumping) that are vital for cell viability [14]. Another major cause of neuronal injury is the release of excitatory neurotransmitters such as glutamate. The extracellular glutamate concentration is normally kept low, powered by the concentration gradients of ions (mainly Na⁺) across the neuronal cell membrane. After stroke, the energy-dependent trans-membrane ion gradients run down, and glutamate transporters reverse their direction, releasing glutamate into the extracellular space. Glutamate acts on receptors in neuronal cells and therefore, produces an influx of calcium that activates enzymes that digest cellular proteins, lipids and nuclear materials. Calcium influx can also lead to the failure of mitochondria, which may cause further energy deterioration. Ischemia also induces production of free radicals and other reactive oxygen species, which may react with and subsequently damage a number of cellular and extracellular elements. In addition to injurious effects on brain cells, the loss of neurovascular structural integrity and functional coupling may also result in neurological dysfunction, a breakdown of the protective blood brain barrier (BBB) that contributes to cerebral edema, which can cause secondary progression of the brain injury [3, 15].

Emerging evidence suggests that ischemic brain damage is a dynamic process that evolves over time. The progression and the extent of ischemic injury are influenced by many factors, including age, severity and location of occlusion,

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state of collateral and systemic circulation, hematological and coagulation factors, body temperature and blood glucose level, etc [16]. Furthermore, acute ischemic tissue often suffers a gradient loss of perfusion, rather than complete and homogeneous ischemia of the entire occluded vessel supplying territory [10]. The key pathophysiological concept is the delineation of ischemic tissue into three operational compartments. Regions suffering the most severe hypoperfusion rapidly progress to irreversible damage and inevitably infarct, representing the ischemic core. The remaining hypoperfused tissue exhibits impairment of the normal blood flow autoregulatory mechanisms and can be pathophysiologically divided into two compartments, namely, salvageable tissue at risk of infarction 'penumbra' and mild ischemic tissue at no immediate risk of infarction 'oligaemia' [17]. The ischemic penumbra was originally described on electrophysiological basis as the tissue existing between the thresholds of electrical failure and ion pump failure [18]. In the ischemic penumbra, oxygen metabolism is preserved and thereby potentially salvageable. Its extent however, decreases over time due to gradual deterioration and as such, represents a key target for therapeutic intervention [19]. Whereas this course of events varies from patient to patient, it has been shown that ischemic penumbra may last for many hours after stroke onset [20]. Timely rescue of the penumbra, either by restoration of blood supply or interruption of the adverse metabolic or neurochemical cascades, is the basis of acute stroke therapy. The benign oligoemic tissue, on the other hand, suffers a mild degree of hypoperfusion with normal oxygen consumption and elevated cerebral blood volume (CBV) and oxygen extraction fraction (OEF), and is not at immediate risk of infarction. If the occlusion persists, however, secondary events such as systemic hypotension, intracranial hypertension or hyperglycaemia may topple this delicate balance and induce the oligoemic tissue to transform into penumbral state and eventually being recruited into the necrotic core [17].

3. MRS CHARACTERIZATION OF ACUTE STROKE

Magnetic resonance spectroscopy (MRS) is capable of studying cellular biochemistry and metabolism by measuring various cerebral metabolites, providing a noninvasive and sensitive means to assess acute ischemic stroke and its progression [21]. Studies of metabolites using proton (^1H) and phosphorus-31 (^{31}P) MRS have enormously contributed to our understanding of cellular metabolism and pathophysiologic processes of cerebral ischemia. Single-voxel based MRS techniques such as point resolved spectroscopy (PRESS) or stimulated echo acquisition mode (STEAM) have been increasingly employed in stroke exams due to its widespread availability and reasonable acquisition time. Recently, there has been great interest in the development of magnetic resonance spectroscopic imaging (MRSI), which can provide information regarding the spatial distribution of metabolites after stroke [22-26] by means of metabolite maps [25], despite moderately longer acquisition time.

Among various metabolites detectable by ^1H MRS, increase in lactate (1.33 ppm) is the most prominent feature of ischemic stroke. Lactate, produced as a metabolic end-product of anaerobic glycolysis after the onset of ischemic

insult, provides a sensitive means for detecting acute stroke [27, 28]. In ^1H MR spectra obtained at short echo time, lactate signal overlaps with lipid peaks (0.9-1.4 ppm), rendering quantitative detection of lactate difficult. Due to the short T_2 relaxation time of lipids, long echo time spectra can suppress the lipid signal and facilitate the measurement of lactate [29]. It is noteworthy that the signal of lactate modulates with echo time due to J-coupling [30], and the lactate doublet peaks are in phase and usually acquired at TE = 136 (inverted) or 272 ms. Apart from lactate, N-acetyl aspartate (NAA; 2.01 ppm) is found to decrease after onset of stroke and continues to decline with time in ischemic lesion [27, 28]. Being highly correlated with histological findings in animal studies, NAA signal decrease indicates neuronal loss or damage after cerebral ischemia [31, 32]. As such, NAA may serve as a metabolic marker in determining early tissue viability. The degree of ischemia and neuronal viability as determined by levels of lactate and NAA, respectively, during acute phase of ischemic stroke has been shown to correlate with the severity of ischemic insult and outcome [33, 34]. Maniega *et al.* demonstrated that temporal evolutions of both lactate and NAA concentrations in stroke patients can provide useful insights into the dynamics of ischemic stroke [35]. Furthermore, it has been suggested that region with near normal NAA but elevated lactate level may represent salvageable ischemic penumbra in acute stroke [25, 36, 37].

^{31}P MRS has been used to study energy states in ischemic stroke by assessing the high-energy phosphorus-containing moieties participating in energy metabolism, particularly ATP and phosphocreatine (PCr) [38-42]. During ischemia, PCr energy buffer decreases with the increase of inorganic phosphate (P_i) in order to maintain ATP homeostasis, and ATP levels decreases once PCr buffer is depleted. In addition, ^{31}P MRS can provide information about intracellular acidosis by determining the difference in chemical shift between the P_i and PCr peaks (δ) as $\text{pH} = 6.72 + \log((\delta - 3.27) / (5.69 - \delta))$ [38, 39, 41, 43].

4. MRI CHARACTERIZATION OF ACUTE STROKE

Commonly used stroke MRI methods include perfusion, diffusion and relaxation MRI. In addition, magnetization transfer (MT) and pH-weighted amide proton chemical exchange saturation transfer (CEST) MRI are also being explored for stroke imaging. It is important to note that whereas computed tomography (CT) is the most utilized method while positron emission tomography (PET) provides more specific characterization of tissue metabolism and perfusion, MRI is widely used due to its multi-parametric diagnosis capability, relatively easy access and non-ionization radiation [8, 11, 13, 44-46].

4.1. Perfusion and Diffusion MRI

Perfusion and diffusion MRI are most commonly used stroke imaging techniques, providing information about disrupted hemodynamic and cellular structural status [17, 47-51]. Whereas MR angiogram can detect the location and severity of occlusion, the downstream tissue hemodynamic status can be better characterized with dynamic susceptibility contrast (DSC), dynamic contrast enhance (DCE) and arterial spin labeling (ASL) techniques, providing quantitative parameters such as cerebral blood flow (CBF),

volume (CBV) and mean transit time (MTT), etc [52, 53]. Particularly, ASL MRI employs arterial water as an endogenous tracer, and is completely non-invasive and very popular in pre-clinical studies [54, 55]. Nevertheless, quantitative perfusion imaging requires assessment of the hemodynamic system such as the arterial input function (AIF) and often assumes intact blood brain barrier (BBB), which may be somewhat oversimplified. Recently, an endogenous imaging technique dubbed modulation of tissue and vessel (MOTIVE) has been proposed to quantify arterial blood volume, which may augment contrast enhanced perfusion MRI [56]. On the other hand, cerebral perfusion is complex and depends on the physiological states and anatomy. Particularly, it has been found that brain white matter (WM) and grey matter (GM) have different perfusion thresholds for ischemia, and a tissue-specific rather than whole brain threshold has been suggested for better prediction of infarction [57].

Diffusion MRI measures the random Brownian motion of water molecules, and has been regarded as one of the most sensitive MRI parameters for imaging stroke [58-63]. It detects ischemic lesion within minutes after hypoperfusion, significantly earlier than the conventional relaxation-based methods [64]. In fact, the development of diffusion-weighted imaging (DWI) has transformed the use of MRI for acute stroke imaging. Specifically, diffusion MRI detects severely injured ischemic tissue while the hypoperfused tissue can be identified with perfusion MRI, leading to the postulation that the mismatch between perfusion and diffusion lesions represents salvageable ischemic tissue [34, 65, 66]. While on the other hand, diffusion lesion, if treated promptly, is reversible yet its long term outcome is rather variable [67-69]. In addition, metabolic impairment within the diffusion lesion has been found to be non-uniform, which may partially explain its heterogeneous outcome [68, 70]. Therefore, the perfusion/diffusion mismatch provides a very useful yet somewhat crude estimation of ischemic penumbra and new surrogate imaging biomarkers are urgently needed to better delineate the heterogeneous ischemic tissue damage [71, 72].

4.2. T_2 and T_2^* MRI

T_2 is a fundamental MRI parameter, sensitive to vasogenic edema and increased water content, and significant T_2 prolongation often suggests irreversible tissue damage [73-75]. T_2 increase in ischemic lesion has also been suggested to be associated with change in magnetization transfer between mobile and immobile proton pools due to structural water alteration [76-78], in which reduced bound water fraction in ischemic tissue leads to T_2 prolongation without significant change in water content. Being highly correlated with established histological and enzymatic techniques, volume with elevated T_2 in late stages has been widely used to estimate final infarct size noninvasively [79, 80]. In addition, Siemonsen *et al.* showed that T_2 difference between infarct core and contralateral brain tissue was highly correlated with the time from symptom onset, allowing estimation of lesion age which is usually unclear clinically [81]. It should be noted that T_2 has been shown to decrease moderately during the initial period of ischemia (hyperacute phase) in which concentration of deoxyhemoglobin increases in areas of hypoperfusion, leading to an increased amount of

spin dephasing of diffusing protons [82-84]. Moreover, transient T_2 normalization during the subacute stage of ischemic stroke has been reported, likely due to transient normalization of water content [85].

T_2^* is another informative MRI parameter that is sensitive to the local blood oxygenation level, known as blood oxygenation level-dependent (BOLD) effect and widely used in functional MRI (fMRI) [86, 87]. Signal change due to the BOLD effect has been observed in acute ischemic stroke using T_2^* -weighted imaging [88-91]. It has been shown that regions of viable yet ischemic brain tissue exhibit decreased T_2^* and T_2' (corrected with spin-spin effects) as a result of an increase in regional deoxyhemoglobin concentration caused by elevated oxygen extraction fraction (OEF) and hypoperfusion [90, 91]. Moreover, T_2^* signal change has been used to detect changes in cerebrovascular reactivity during and after transient ischemia to assess tissue damage in animals. Ono *et al.* illustrated that impaired CO_2 reactivity after transient ischemia revealed irreversible ischemic damage, whereas recovered CO_2 reactivity during reperfusion indicated absence of pathological damage [92]. Furthermore, Santosh *et al.* demonstrated that in permanent middle cerebral artery occlusion (MCAO) model, areas with increased T_2^* signal indicate oxygen utilization, which is viable and metabolically active, while areas without significant T_2^* signal change suggest severely disrupted metabolism and are likely severely damaged [93].

4.3. pH-weighted MRI

Whereas tissue pH can be assessed by ^{31}P MRS and to some extent, lactate MRS, their spatiotemporal resolution is limited and not suitable for routine examination of acute stroke patients [94-97]. To address this, pH imaging has been developed, based on the principle of chemical exchange saturation transfer (CEST) MRI [98]. CEST MRI is an emerging MRI method capable of detecting dilute labile proton groups and local pH [99-104]. In particular, amide proton transfer (APT) MRI, a specific form of CEST MRI that probes pH-dependent amide proton exchange from endogenous mobile proteins and polypeptides, offers a non-invasive pH imaging technique for characterizing ischemic acidosis [102, 105, 106]. Noteworthy, the sensitivity of pH MRI is significantly higher than MRS-based methods (e.g., lactate and ^{31}P MRI), and permits pH mapping at spatiotemporal resolution comparable to that of ASL MRI [103, 107].

Both numerical simulation and empirical solutions have been developed to guide optimization and quantification of CEST MRI since the pioneering work of Balaban *et al.* [108-112]. pH-weighted APT MRI has been translated to image ischemic acidosis, an early marker of impaired tissue metabolism [113-115]. Specifically, Sun *et al.* established a dual 2-pool mathematical model to describe *in vivo* APT MRI during acute stroke, and quantified the endogenous mobile amide proton concentration and exchange rate [109, 116]. In addition, pH-weighted APT MRI lesion detects not only severely injured ischemic lesion that shows diffusion abnormality, but also ischemic lesions with T_2 hypointensity, a surrogate marker for altered oxygen metabolism [91, 93]. Moreover, it has been suggested that pH-weighted APT MRI

can better predict stroke outcome, in complementary to the commonly used perfusion and diffusion MRI [117]. Recently, Jokivarsi *et al.* also showed that pH-weighted APT contrast correlates with lactate MRS [118]. In addition, we have demonstrated that the correlation between endogenous APT contrast and lactate content can be enhanced with T_1 -normalized APT MRI, consistent with the fact that APT/CEST contrast approximately scales with T_1 . Nevertheless, *in vivo* APT MRI is complex. In addition to pH-weighted APT contrast, it is also susceptible to concomitant RF irradiation effects, slightly asymmetric semisolid macromolecular magnetization transfer (MT) and nuclear overhauser effect (NOE), which have to be further investigated for quantitative pH imaging [119-121]. Noteworthy, pH MRI may be suitable for studying transient ischemic attack (TIA). For instance, Sicard *et al.* showed that despite full recovery of perfusion and diffusion images, animals with transient MCAO (tMCAO) showed delayed normalization in behavior and fMRI, suggesting prolonged neuronal damage [122]. Similarly, Bisschops *et al.* reported that although the neurological deficits of TIA patients are transient, their metabolic changes are present days after the onset of symptoms, and not limited to the symptomatic hemisphere [123]. Therefore, multi-parametric characterization of tissue metabolic status such as tissue pH and lactate may provide new insights into TIA. While on the other hand, whereas endogenous APT MRI has been shown capable of detecting ischemic acidosis 24 hr after MCAO, its contrast is very complex due to proteolysis, change in tissue temperature and relaxation times [106, 117, 124]. To address this limitation, additional mathematical modeling is needed to delineate tissue pH from the confounding amide proton concentration effect [102, 125].

4.4. Sodium MRI

Sodium (Na) MRI offers a very promising imaging technique to examine tissue viability [126]. Well regulated sodium balance is vital for cell viability: the cytoplasm has low sodium yet high potassium concentration, in contrast to interstitial space. The regulation of sodium and potassium depends on ATP dependent active transporters, which dysfunctions upon membrane depolarization during ischemia [127, 128]. Subsequently, cytoplasm sodium level increases significantly, which may serve as a specific marker for metabolic disruption and cell viability [129]. Whereas T_2 of sodium MR signal is very short, twisted projection imaging (TPI) has been developed that permits three-dimensional acquisition of sodium imaging *in vivo* [130]. In addition, intracellular sodium can be differentiated from interstitial space using double quantum filter, which may further improve the specificity of sodium imaging. Moreover, it has been shown that the total sodium concentration may serve as a tissue clock for estimating stroke onset time, aiding stroke treatment [131, 132].

5. MULTI-PARAMETRIC IMAGE ANALYSIS

Due to the dynamic nature of ischemic tissue damage, a single MRI parameter often has its own time window to reveal the abnormality, and thus may not fully characterize the ischemic tissue injury [133]. For instance, ADC declines rapidly within minutes of ischemic stroke, but it pseudo-normalizes and even rises above the normal range in latter

stages [68]. Therefore, the multi-parametric MRI analysis is necessary to assess the heterogeneous ischemic tissue damage [13, 134]. Specifically, methods including generalized linear model (GLM), K-means, fuzzy c-means, and interactive self-organizing data analysis technique algorithm (ISODATA) segmentation with multi-parametric MRI have been suggested for ischemic tissue classification [44, 135, 136]. In particular, ISODATA is an unsupervised segmentation algorithm based on cluster analysis which can recognize structures within a data set and automatically determine the number of clusters [137]. Multiple tissue signatures can be segmented from the data set by ISODATA, generating a theme map that reflects different tissue clusters [138]. Studies have shown that ISODATA technique can accurately define the ischemic region which was well correlated with histologically determined lesion at different stages after stroke [136, 139], and ISODATA lesion volume at acute stage has strong correlation with stroke outcome [138, 140]. Increasing the dimensionality of the ISODATA model by incorporating additional images has been shown to better demarcate tissue clusters [139, 141]. Moreover, the heterogeneity within the ischemic lesion in the ISODATA theme map has been suggested to indicate heterogeneous tissue damage [142]. Furthermore, Shen *et al.* showed that employing statistical algorithm following ISODATA tissue clustering can help improve the prediction of the ischemic tissue outcome in animal models [143, 144]. Specifically, a training data set was used to derive the probability profiles of tissue fate pixel-by-pixel, which were then applied to generate maps of risk of subsequent infarction. Such a predictive approach has been shown to improve the predication in transient stroke by taking into account of the regional susceptibility to infarction [144]. More recently, predictive algorithm based on artificial neural network has also been developed for prediction of ischemic tissue fate based on multiparametric MRI data [145]. These predictive models, if fully developed, may greatly aid clinical decision making in the treatment of acute stroke by providing objective predictions of ischemic tissue fates.

6. CONCLUSIONS AND PROSPECTS

MRI and MRS techniques have greatly improved our understanding of stroke pathophysiology. In addition, emerging MR techniques are being developed to capture new facets of ischemic tissue damage with enhanced sensitivity and specificity. Such a breadth of information can be characterized with multi-parametric analysis tools for improved tissue classification. Most importantly, further development and validation of MR techniques and image analysis tools may help establish imaging-based outcome prediction algorithms and ultimately, guide individualized stroke treatment.

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